

Conferences and Reviews

Female Urethral Syndrome A Female Prostatitis?

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The cause of the female urethral syndrome has previously been obscure, as it has been associated by definition with a lack of objective findings but a plethora of subjective complaints of retropubic pressure, dyspareunia, urinary frequency, and dysuria. There is now strong evidence that the microscopic paraurethral glands connected to the distal third of the urethra in the prevaginal space are homologous to the prostate. They stain histologically for prostate-specific antigen and, like the prostate, are subject to both infection and cancer. The most important aspect of recognizing this microscopic "female prostate" as an anatomic feature is that its infections may completely explain many cases of the urethral syndrome. Further, the diagnosis is not elusive if trained clinicians palpate for localized and objective paraurethral tenderness through the anterior vagina wall to one or both sides of the urethra. Treatment parallel to that for male prostatitis is usually rewarded by the elimination of symptoms and the objective finding of the loss of tenderness of the paraurethral glands. As with prostatitis, the localized problem often recurs. It is time to alert primary care physicians to this disorder and to eliminate the widespread practice of treating affected women with either invasive urethral dilation or tranquilizers.

(Gittes RF, Nakamura RM: Female urethral syndrome—A female prostatitis? *West J Med* 1996; 164:435-438)

For 30 years, the urethral syndrome has been a catchall diagnosis for the frequently seen women who have symptoms resembling a lower urinary tract infection but whose objective findings are negative—that is, no abnormal midstream urinalysis findings, no positive bacterial culture, and no obvious finding on a pelvic examination.^{1,2} Similar symptoms in a man would suggest prostatitis and would lead to microscopic examination of the prostatic secretions for the presence of inflammatory cells.³ Is there a "female prostate" to also investigate?

'Female Prostate'

For many years, anatomists have described homologues of the prostate in the little glands adjacent to the female urethra. These were first described by Regeneri de Graaf in 1672.⁴ In 1880 Skene described the two main ducts that bear his name and that drain the most distal of the glands to their openings, which are adjacent to the meatus of the female urethra.⁵ These were anatomical curiosities until the late 1940s and 1950s, when Huffman made careful serial sections and reconstructions to describe the female paraurethral glands branching out from the urethral lumen into the adjacent soft tissue alongside the distal two thirds of the urethra (Figure 1).^{6,7} He noted columnar epithelium that stained with mucicarmine. He wrote that, in postmortem tissues, "inflam-

matory reactions in and about the ducts and glands are common."^{6(p97)}

In a scholarly dissertation, Huffman related that paraurethral ducts and glands play an important role in nonspecific urethritis, including the occasional abscess or cysts that may develop into a female urethral diverticulum. He also described adenomas and rare adenocarcinomas arising from these glands.

Long before Huffman's work, the role of the paraurethral glands had been discounted. Cabot and Shoemaker dismissed the glands themselves as simply invaginations of the urethral mucosa and suggested that glands of the female urethra, except Skene's glands, do not play an important role in infections of the female urinary tract.⁸ The work of Huffman, reported in the gynecologic literature, did not affect the practice of urologists who were by then converted to an obstructive interpretation of female urethral problems and practiced aggressive urethral dilatations and surgical urethrotomies for recurrent urethral symptoms.⁹⁻¹¹ A lone exception among urologists was one who advocated visualization of the openings of the paraurethral ducts and with a tiny probe slicing them open with electrocautery into the urethral lumen, with anecdotal uniform "success."¹²

In the past decade, the availability of the specific histochemical staining for prostate-specific antigen (PSA) has rehabilitated the status of the paraurethral glands and

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This work was supported in part by a grant from the Neilson Brown Fund at Scripps Clinic and Research Foundation.

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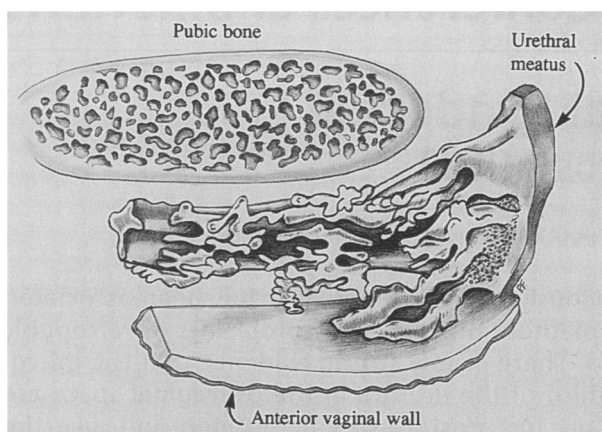


Figure 1.—A 3-dimensional reconstruction from histologic serial sections of normal female urethra is shown. The paraurethral ducts and glands are invariably found alongside the distal two thirds of the urethra (from Huffman⁶).

spotlighted them as the homologue of the prostate.¹³⁻¹⁵ Earlier research on the small rodent *Mastomys natalensis* had been reported in which a well-defined “prostatic gland” was described in all of the female animals.¹⁶ These rodents have been recently used as an animal model for chronic bacterial prostatitis in both male and female animals with *Escherichia coli*.¹⁷

The rare clinical adenocarcinomas of the distal female urethra are now recognized as primary tumors of the “female prostate” due to their specific staining with PSA and prostate-specific acid phosphatase.¹⁸⁻²⁰

Urethral Syndrome

The term “urethral syndrome” has been used for nearly 30 years to describe a condition that occurs in a large number of women who present with symptoms of retro-pubic pressure, urinary frequency, and dysuria, often with dyspareunia, but who on examination do not have either vaginal infection or cystitis as determined by cultures and colony counts of midstream urine specimens.¹ Urologic textbooks have had to deal with this disorder for years because it is recognized that the patients who are so labeled form a large part of the outpatient practice of general physicians and gynecologists and even more so of urologists who are referred untreated or unresolved chronic cases.² In one gynecologic review, it was estimated that more than 5 million office visits per year were for this problem.²¹ An astounding variety of treatments have been practiced over the years, covering the full spectrum from aggressive surgical excision of the peri-urethral tissue,¹⁰ internal urethral cutting procedures, and forceful overdilations of the urethra^{9,11,12} to the use of anxiolytic and tricyclic antidepressant drugs (“tranquilizers” [diazepam, amitriptyline]) as the sole treatment. This last therapy has been based on the idea that the women had functional complaints with pelvic floor muscle spasm.^{22,23} In the only prospective study of treatment alternatives, short courses of the urinary antibiotics nitrofurantoin and the combination of trimethoprim and sulfamethoxazole

were included, as well as anticholinergic agents and urethral dilations, with no treatment controls.²⁴ Although all treatments were judged ineffective and it was suggested that treatment be supportive and “harmless,” aggressive management continues to be widely practiced today.

In a chapter dealing with this syndrome in a textbook of urology, Messing stressed that the diagnosis was one of excluding other disorders that have objective findings.² He further commented that “pelvic examination (with the possible exception of mild anterior distal vaginal tenderness) . . . must reveal no abnormalities that could explain the symptoms.”^{22(p1087)} The textbook answer to the cause of the urethral syndrome has continued to be uncertain, with a menu of obstructive, infectious, neurogenic, and psychogenic possibilities being offered.^{24(p1087)} The role of the infection that has been repeatedly investigated was challenged by the lack of polymorphonuclear leukocytes in the urine and the low bacterial colony counts in contrast to the findings associated with overt cystitis. Experts in urinary infection attempted to define offending organisms and recognized that antibiotic therapy was empirically effective.^{25,26} *Chlamydia* species were found in the urethra of young women.²⁵ Even the possibility of fastidious organisms has been indicated.²⁷ But none of the recent investigators have correlated the diagnosis of the infection to the anatomically cryptic paraurethral glands.

The possible psychogenic cause that has been used as the basis for treatment with anxiolytic drugs for the past 20 years has been supported by various publications studying the response of such patients to personality tests (Minnesota Multiphasic Personality Inventory),²⁸ measurements of pelvic floor tension,²² or external sphincter reactivity.²³ A recent psychological study sagely suggests that perhaps these were normal women responding to the stress of continuing symptoms and inadequate diagnosis and treatment.²⁹

The advanced imaging technology with internal vaginal ultrasonography was applied to patients with the urethral syndrome by a Japanese group.³⁰ This group reported no imaging differences from those of controls, but rather the simple finding that “tenderness at the upper frontal wall of the vagina was seen in 10 of 11 patients with urethral syndrome . . . and in 1 of 9 with a normal bladder.”^{30(p1094)} They concluded that “internal examination for tenderness at the frontal wall of the vagina” was “useful for diagnosis and follow-up of the patients with urethral syndrome.”^{30(p1094)} No correlation of this tenderness with the paraurethral glands was recognized.

Diagnosis by Pelvic Examination

Rather than using a diagnosis of exclusion, as in the past, we have relied on a careful pinpoint palpation of the soft tissue of the anterior vaginal wall on each side of the urethra to make a clinical diagnosis of infection of the paraurethral glands in cases that would otherwise fall into the category of urethral syndrome. As shown in Figure 2, digital examination of the small volume of tissue involved by this symptomatic inflammation permits a strong presumptive diagnosis of infection of the paraurethral

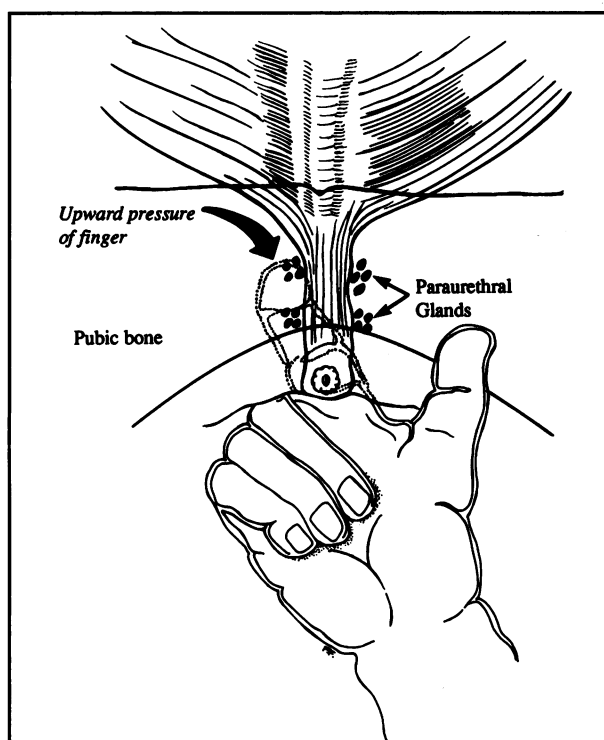


Figure 2.—Upward fingertip pressure against the pubic bone lateral to the urethra elicits localized tenderness when the paraurethral glands are infected.

glands. The examination certainly parallels a digital rectal examination that finds localized prostate gland tenderness that is then treated with antibiotics as a prostatitis. Of course, fluid is not available for expression by massage and microscopic analysis, so treatment becomes empirical on the basis of these localized findings. More invasive diagnostic maneuvers do not appear justified.

Treatment of Female Prostatitis

The treatment of the detected tenderness of the paraurethral glands is based on the same premises that clinicians use in the treatment of men with prostatic infections. First, the paraurethral glands and any organisms within them are isolated from therapeutic concentrations of antibiotics in the urine, requiring tissue-penetrating agents. Second, the relative inaccessibility and presumed stagnation of the glands may require long-term treatment with tissue-penetrating antibiotics to achieve a cure.

Because of the findings of investigators characterizing the small number of organisms that reach the urethral lumen,²⁵ younger women are treated with tetracycline or erythromycin on the presumption that they have *Chlamydia* species in those glands. They are treated for two to four weeks. Older women or younger women for whom the first treatment fails are given a quinolone for at least a month.³¹ Hot sitz baths are also advised and seem to help during the acute phase (as in male prostatitis).

Antibiotic treatment usually eliminates the symptoms. An objective vaginal reexamination in follow-up

usually confirms the decrease or absence of tenderness in the specific areas in the anterior vaginal wall. Conversely, as in prostatitis, relapses may occur months or years later, and at that time the specific findings on physical examination will also return.

Anatomic Studies

We obtained several specimens of female urethra and its surrounding soft tissue en bloc from brain-dead donors undergoing harvesting of multiple organs for transplantation. Serial sections, transverse and longitudinal, consistently revealed the presence of the paraurethral glands and confirmed the positive staining for PSA. One case of an older woman who died of a sudden cerebral hemorrhage serendipitously yielded examples of paraurethral glands with active inflammation (Figure 3). The appearance would be parallel to that seen in the histologic examination of a biopsy specimen in a case of prostatitis.

Because prostatitis is capable of raising the systemic blood level of PSA in men, we tested to see if women affected with severe inflammation of the paraurethral glands would reflect an elevation of PSA levels in their blood. Blood specimens taken before and after palpation of the tender glands were studied by an ultrasensitive

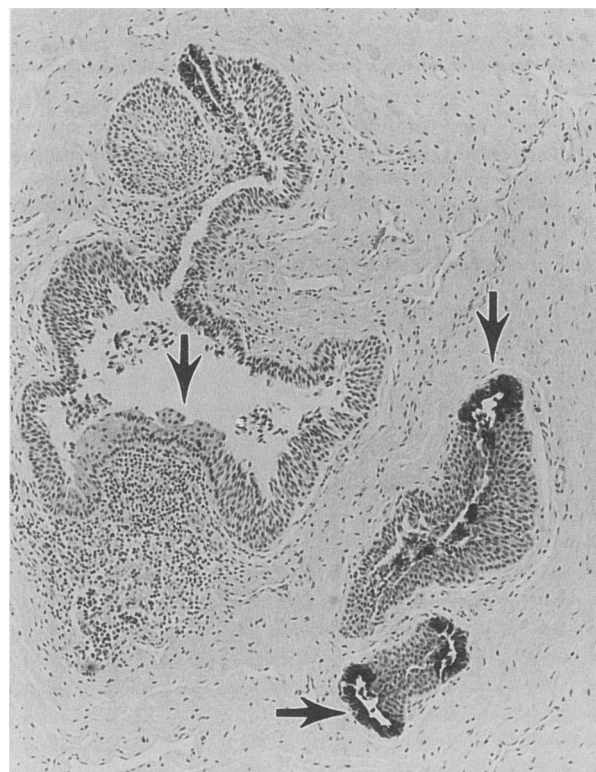


Figure 3.—A cross-section of paraurethral glands obtained from a cadaver organ donor is shown. Submucosal and luminal inflammation was demonstrated (left arrow). Reactivity with anti-prostate-specific-antigen antibody is absent in the inflamed gland but well shown in 2 adjacent smaller glands (right arrows). (Immunoperoxidase stain with hematoxylin counterstain, original magnification $\times 125$.)

PSA immunoassay (Abbott Laboratories, Chicago, Ill), but in all the PSA was undetectable.

Conclusion

In retrospect, it seems likely that clinicians have been overlooking specific infections of the microscopic female paraurethral gland and labeling such cases as the urethral syndrome. Such female prostatitis is common and should be diagnosed by a careful pelvic examination by the initial examining physician or other trained medical personnel. Treatment commensurate with the extraurinary location of the inflamed tissue, as in the male prostate, will give gratifying results, and its success can then be confirmed objectively by reexaminations. The finding and treatment of female prostatitis may eliminate a large portion of the cases of urethral syndrome and abrogate the condescending management of such women with either dilations or anxiolytic drugs.

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